# Increased Risk of Preterm Birth from Intrauterine Exposure to Mediators of Inflammation

**Intrauterine exposure to mediators of inflammation** due to infection of either vaginal, cervical, or uterine sites, or of more distal sites (e.g., periodontal disease) is associated with an **increased risk of preterm birth.**

| General Information | |
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| **Broad Focus Area** | Undesirable outcomes of pregnancy: birth defects and preterm birth |
| **Background and Justification** | While the cause of most preterm births is unclear, evidence of placental or chorioamniotic infection is present in up to 40% of all spontaneous preterm births and in up to 75% of those born before 32 weeks gestation--the infants at greatest risk of subsequent adverse outcome.[1,2] Numerous common organisms of generally low virulence (e.g., ureaplasma, mycoplasma, gardenerella) have been associated with spontaneous preterm birth. Chorioamniotic or vaginal markers of inflammation and infection have been associated with preterm birth in the absence of identifiable infectious agents. In addition, potential associations between periodontal disease and preterm birth have recently been reported.[3] |
| **Prevalence/ Incidence** | Each year in the US, approximately 12% of all births are preterm (<37 weeks gestation).[4] Two-thirds of all infant deaths in the US occur among those born preterm; preterm birth is associated with substantial neonatal morbidity, a high risk of long-term neurodevelopmental deficits, and low academic achievement.[5] In term pregnancies, about 1-2% are affected by chorioamnionitis (intrauterine infection); in pregnancies ending in preterm births, the prevalence of such infection is higher.[6] |
| **Economic Impact** | A report based on 1988 data estimated an annual incremental increase of $6 billion in health care, education, and child care costs attributable to children <15 years born low birth weight (LBW), compared to if they had been normal-birthweight[7] (69% of LBW children are born preterm).[8] This underestimates current costs because of increasing preterm birth rates and improved survival of preterm infants. Due to large socioeconomic and racial or ethnic disparities, the US population does not evenly share the medical, educational, and economic costs of preterm births. |

| Exposure Measures | | | Outcome Measures | |
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| ***Primary/ Maternal*** | Maternal infection/inflammation:<br>- Infection serology (lymphocytes, antibodies, cytokines/ interleukins, inflammatory markers)<br>- Cultures (cytokine; metalloproteinase)<br>- Medical history of fever and infection (medicine usage) during pregnancy<br>- Dental exams | | ***Primary/ Maternal*** | |
| Methods | - Blood samples<br>- Vaginal/cervical cultures<br>- Examination by a medical professional | | Methods | |

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| | - Interview<br>- Medical record review | | | |
| Life Stage | Prenatal | | Life Stage | |
| ***Primary/Child*** | Prenatal infection:<br>- Umbilical cord/placental culture (antibodies; cytokines) | | ***Primary/Child*** | Preterm birth:<br>- Gestational age; birth weight |
| Methods | - Physical sampling at delivery<br>- Placental culture/exam at birth | | Methods | Examination by a medical professional |
| Life Stage | Birth | | Life Stage | Birth |

| Important Confounders/Covariates | |
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| Economic status | Increased risk associated with low educational level; unmarried status[9] |
| Race/ethnicity | As a percent of live births, 17.6% among Blacks are preterm, 11.4% among Hispanics, and 10.8% among Whites.[10] |
| Mother's medical history | Increased risk associated with maternal smoking, alcohol consumption; older maternal age (indicated preterm births); younger maternal age (spontaneous preterm births); low or high parity; previous stillbirth[11, 12, 13] |
| Others | Increased risk associated with caffeine consumption; unwantedness of the pregnancy[14, 15] |

| Population of Interest | | Estimated Effect that is Detectable |
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| All pregnant women and their offspring | | Assuming a sample size of 100,000 pregnancies, incidence of very preterm birth (<32 weeks) of 2%, and prevalence of intrauterine infection of 2%, the smallest detectable relative risk will be approximately 1.5. |

***References:***


[1] Romero R, Espinoza J, Chaiworapongsa T, Kalache K. (2002). Infection and prematurity and the role of preventive strategies. Semin Neonatol. 2002;7:259-74.

[2] Andrews WW, Hauth JC, Goldenberg RL. (2000). Infection and preterm birth. Am J Perinatol. 2000;17:357-65.

[3] Offenbacher S, Jarod HL, O'Reilly PG ,et al. (1998). Potential pathogenic mechanisms of periodontitis associated pregnancy complications. Ann Periodontal. 1998;3:233-50.

[4] Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM. (2002). Births: Final data for 2000. National Vital Statistics Reports; vol 50, no 5. Hyattsville, MD: National Center for Health Statistics. 2002.

[5] Hack M, Flannery DJ, Klein N, et al. (2002). Outcomes in young adulthood for very-low-birth-weight infants. N Engl J Med. 2002;346:149-57.

[6] Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. JAMA. 2000 Sep 20;284(11):1417-24.

[7] Lewitt EM, Schuurmann Baker L, Corman H, Shiono P. (1995). The direct cost of low birth weight. Future Child.1995;5:35-56.

[8] Savitz DA, Ananth CV, Berkowitz GS, Lapinski R. Concordance among measures of pregnancy outcome based on fetal size and duration of gestation. Am J Epidemiol. 2000 Mar 15;151(6):627-33.

[9] Effects of maternal cigarette smoking on birth weight and preterm birth—Ohio, 1989. 1990. MMWR Morb Mortal Wkly Rep. 28 Sep 1990; 39(38):662-5.

[10] Division of Vital Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

[11] Heffner LJ, Sherman CB, et al. 1993. Clinical and environmental predictors of preterm labor. Obstet Gynecol. May 1993; 81(5 (Pt 1)):750-7.

[12] Meis PJ, Michielutte R, et al. 1995. Factors associated with preterm birth in Cardiff, Wales. II. Indicated and spontaneous preterm birth. Am J Obstet Gynecol. Aug 1995; 173(2):597-602.

[13] Wisborg K, Henriksen TB, et al. Smoking during pregnancy and preterm birth. Br J Obstet Gynaecol. Aug 1996;103(8):800-5.

[14] Olsen P, Laara E, et al. 1995. Epidemiology of preterm delivery in two birth cohorts with an interval of 20 years. Am J Epidemiol. 1 Dec 1995; 142(11):1184-93.

[15] McDonald AD, Armstrong B, et al. 1992. Cigarette, alcohol, and coffee consumption and prematurity. Am J. Public Health. Jan 1992; 82(1):87-90.